C5 cont.

60 ~~63~~ (new). The DNA segment of claim 1, wherein the nucleic acid segment comprises the nucleotide sequence of SEQ ID NO: 50.

61 ~~64~~ (new). A composition comprising the DNA segments of any one of claims 1, 11, 12, 21, or 22 and a pharmaceutically acceptable excipient.

REMARKS

Upon entry of the present amendments, claims 1, 11, 12, 21-30, 36, 37, and 52-64 will be pending and under active consideration in the above-identified patent application. Claims 2-10, 13, 14, 16-20, 31-34, and 44-48 have been canceled without prejudice. Claims 11, 12, 21, 22, 23, 24, 25, 26, 27 and 36 have been amended to more clearly claim the invention as disclosed in the specification.

Claim 1 has been amend to recite a DNA segment comprising an isolated nucleic acid, wherein said nucleic acid comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:28; SEQ ID NO:30; SEQ ID NO:32; SEQ ID NO:34; SEQ ID NO:36; SEQ ID NO:38; SEQ ID NO:40; SEQ ID NO:42; SEQ ID NO:44; SEQ ID NO:46; SEQ ID NO:48; and SEQ ID NO:50. Support for the amendment to claim 1 can be found, *inter alia*, at page 78, line 18 to page 83, line 19.

Claims 11, 12, 21, 22, 24 and 26 have been made independent. Claims 23, 27 and 36 have been amended to correct the claim dependency.

New claims 52-64 have been added. Support for the newly added claims is found throughout the specification as originally filed. No new matter has been added by the amendments to the claims.

1. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 31-33 and 47-48 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants do not agree with the Examiner's rejection and in no way acquiesce to this rejection or to the basis on which it is made. However, claims 31-33 and 47-48 have been canceled without prejudice. Applicants fully reserve all rights to the subject matter of claims 31-33 and 47-48 and intend to pursue such

subject matter is a related application. In addition, Applicants fully reserve all rights to respond to this rejection should it be raised in any subsequent application. Thus, in view of the cancellation without prejudice of claims 31-33 and 47-48, this Section 112, first paragraph, rejection has been obviated and Applicants respectfully request its removal.

2. Rejection Under 35 U.S.C. § 103

Claims 1, 2, 8, 10, 13, 16, 20-30, 34, 36, 37 and 44-48 are rejected under 35 U.S.C. § 103(a) allegedly as being obvious over Fung et al., 1987, Science 236:1657-1660 ("Fung") in view of EP 259 031 to Dryja et al. ("Dryja") and Friend et al., 1987, Proc. Natl. Acad. Sci. USA 84:9059-9063 ("Friend"). The Examiner contends it would have been obvious to one of skill in the art at the time of the claimed invention to modify and make deletions in the N-terminal region of RB protein using the DNA taught by Dryja or Friend, and make vectors and study their effect on the growth of transformed cells with a reasonable expectation of success.

Applicants respectfully disagree with the Examiner's rejection. The rejected claims are directed to DNA segments comprising specific nucleotide sequences encoding a modified retinoblastoma tumor suppressor proteins, which proteins have substantially equivalent biological activity as compared to the wild-type retinoblastoma protein. Applicants point out that there is no hint or suggestion in the cited references, alone or in combination, of the identity of the specific modified proteins. Thus, the nonobviousness of the claimed invention is apparent.

The DNA disclosed in Dryja or Friend cannot render obvious the specific DNA segments of the presently claimed invention either alone or in combination with any other reference.

The Examiner's attention is directed to *In re Deuel*, 51 F.3d 1552; 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995), which overturned a Board of Patent Appeals and Interference determination of obviousness. In *In re Deuel*, the Court held that claims directed to purified and isolated DNA encoding human (or bovine) heparin binding growth factor were not obvious in view of a reference disclosing a brain-derived heparin-binding protein and its N-terminal sequence together with a reference describing general cloning methods.

The Court explained that although the general idea of the claimed molecules, their function and general chemical nature may have been obvious from the cited references, and the "knowledge that some gene existed may have been clear", the claimed DNA molecules would not have been obvious. "[U]ntil the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious." *In re Deuel*, 51 F.3d at 1558, 34 U.S.P.Q.2d at 1215. Similarly to the situation in *Deuel*, until the actual claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. Therefore, the fact that other modified retinoblastoma nucleic acids were known cannot render obvious the claimed subject matter. As stated by the Court:

> [A]ny motivation that existed was a general one, to try to obtain a gene that was yet undefined and may have constituted many forms. A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search. *Deuel*, *Id.*

Further, "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out". *Deuel*, 51 F.3d at 1559, 34 U.S.P.Q. at 1559, 1216. "The fact that one can conceive a general process in advance for preparing an unidentified compound does not mean that a claimed specific compound was precisely envisioned and therefore obvious" *Id.*

Moreover, as explained by the Court, "[t]he PTO's focus on known methods for potentially isolating the claimed protein molecules is also misplaced because the claims at issue define compounds, not methods." In fact, the Court stated:

> [T]he existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence or prior art that suggests the claimed DNAs.
>
> . . .
>
> Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious a particular claimed cDNA. "Obvious to try" has

> long been held not to constitute obviousness. A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out (citations omitted).

Deuel, 51 F.3d at 1559, 34 U.S.P.Q.2d at 1215-1216. See also, *Amgen, Inc. v. Chugai Pharmaceutical, Co., Inc.*, 927 F.2d 1200; 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991).

Therefore, since the claimed products of the present invention could not have been conceived or contemplated before their actual isolation and purification, they are nonobvious. In view of the foregoing, the nucleic acids disclosed by Fung, Dryja and/or Friend, alone or in combination, cannot render obvious the claimed compositions of the present invention. Applicants submit that the Examiner is engaging in the impermissible use of hindsight to formulate the rejection. It is impermissible to engage in hindsight reasoning, using the claims as a frame and the prior art references as a mosaic to piece together a facsimile of the claimed invention. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

In view of the foregoing, Applicants submit that the Examiner's rejection is in error and respectfully request its withdrawal.

3. Objections to the Claims

Claims 3-7, 9, 11, 12, 14, 15, and 17-19 have been objected to for being dependent on rejected claims. In response, Applicants note that in view of the amendments to the claims made herein, the objection has been obviated and/or overcome, and thus, should be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the present application. Claims 1, 11, 12, 21-30, 36, 37 and 52-64 fully meet all statutory requirements for patentability and non-obviousness. Withdrawal of the Examiner's objection and rejections is respectfully requested.

Applicants respectfully request that the Examiner call the undersigned at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

Date: October 10, 2002

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EXHIBIT A

Serial No. 09/026,459
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Attorney Docket No. 8660-025

MARKED-UP VERSION OF CLAIMS
UNDERLINED TEXT IS ADDED AND [BRACKETED TEXT] IS DELETED

1 (thrice amended). A DNA segment comprising an isolated [gene encoding a modified retinoblastoma tumor suppressor protein other than pRB^{94} or pRB^{56}, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not consist of a deletion or substitution of amino acids 184-192 or 245-262 , which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein] nucleic acid, wherein said nucleic acid comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:28; SEQ ID NO:30; SEQ ID NO:32; SEQ ID NO:34; SEQ ID NO:36; SEQ ID NO:38; SEQ ID NO:40; SEQ ID NO:42; SEQ ID NO:44; SEQ ID NO:46; SEQ ID NO:48; and SEQ ID NO:50.

11 (once amended). The DNA segment [of claim 10, wherein] comprising an isolated nucleic acid , said nucleic acid encoding a modified amino acid sequence of SEQ ID NO:2, wherein said modification is that amino acid 2 through amino acid 34, and amino acid 76 through amino acid 112 have been deleted.

12 (once amended). The DNA segment [of claim 10, wherein] comprising an isolated nucleic acid , said nucleic acid encoding a modified amino acid sequence of SEQ ID NO:2, wherein said modification is that amino acid 2 through amino acid 55, and amino acid 76 through amino acid 112 have been deleted.

21 (twice amended). The DNA segment [of claim 2, wherein said gene] comprising an isolated nucleic acid, which nucleic acid encodes a modified retinoblastoma tumor suppressor protein consisting of the contiguous amino acid sequence of SEQ ID NO:29; SEQ ID NO:31; SEQ ID NO:33; SEQ ID NO:35; SEQ ID NO:37; SEQ ID NO:39; SEQ ID NO:41; SEQ ID NO:43; SEQ ID NO:45; SEQ ID NO:47; SEQ ID NO:49; or SEQ ID NO:51.

22 (twice amended). The DNA segment [of claim 2, wherein said gene consists of] comprising an isolated nucleic acid, wherein said nucleic acid comprises the contiguous nucleic acid sequence from between position 7 and position 2691 of SEQ ID NO:28; from between position 7 and position 2628 of SEQ ID NO:30; from between position 7 and position 2559 of SEQ ID NO:32; from between position 7 and position 2502 of SEQ ID NO:34; from between position 7 and position 2349 of SEQ ID NO:36; from between position 7 and position 2559 of SEQ ID NO:38; from between position 7 and position 2697 of SEQ ID NO:40; from between position 7 and position 2583 of SEQ ID NO:42; from between position 7 and position 2397 of SEQ ID NO:44; from between position 7 and position 2613 of SEQ ID NO:46; from between position 7 and position 2619 of SEQ ID NO:48; or from between position 7 and position 2790 of SEQ ID NO:50.

23 (twice amended). The DNA segment of claim 1, 21, or 22, operationally linked under the control of a promoter.

24 (once amended). [The] A recombinant vector comprising the DNA segment of claim 23 [contained within a recombinant vector].

25 (once amended). The [DNA segment] vector of claim 24, [wherein said recombinant vector is contained within] which is an adenoviral vector.

26 (once amended). A recombinant adenovirus comprising the [The] DNA segment of claim [25, wherein said adenoviral vector is contained within a recombinant adenovirus,] 23.

27 (twice amended). The DNA segment of claim 1, 21, or 22, recombinantly transformed into a host cell.

36 (once amended). A recombinant host cell comprising a DNA segment [comprising an isolated gene encoding a modified retinoblastoma tumor suppressor protein other than pRB^{94} or pRB^{56}, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not consist of a deletion or substitution of amino acids 184-192 or 245-262, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein] of any one of claims 1, 11, 12, 21, or 22.